UNIVERSITY OF OKLAHOMA MEDICAL CENTER

CORRELATION OF POOLING AND RESISTANCE CHANGES IN THE CANINE FORELIMB IN SEPTIC SHOCK

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Technical Report No. 34
University of Oklahoma Medical Center THEMIS Contract

MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE
OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.
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Research in endotoxin shock has emphasized mechanisms eliciting early, delayed, and sustained systemic hypotension in various sub-human experimental shock models (3-9, 11, 12, 14). It appears that a primary mechanism in the canine species is early hepatosplanchnic pooling of blood (5, 11, 12, 14) which decreases venous return and cardiac output, resulting in a drop in arterial pressure. Intra- and extra-vascular pooling of blood after endotoxin has been suggested to be due in part to generalized venous constriction in various vascular beds (4, 5, 9, 12, 14).

The canine forelimb perfused at constant arterial inflow shows a progressive weight increase after endotoxin administration which occurs concommitantly with elevations in arterial and venous segment resistances (4). Limb weight falls markedly, however, in a similar preparation perfused at natural flow (7). The differences in responses between these studies may be explained on the basis of the higher maintained flow rate in the presence of sustained venous constriction in the former preparation (4) creating an obstructive phenomenon. However, since changes in capillary hydrostatic pressure depend of alterations in the ratio between pre- and post-capillary resistance, pooling in the limb in endotoxin shock might result if this ratio were to decrease significantly (2, 10, 13).

Mellander and Lewis have reported an impairment of the responses of resistance and capacitance vessels and cat muscle during hemorrhagic shock (13). They found that the pre- to post capillary resistance ratio decreased after neuro-humoral stimulation, resulting in a net outward movement of capillary fluid. They postulated that the increase in post-capillary resistance in shock may outlast or overbalance that of the pre-capillary segment, thus resulting in pooling upstream from constricted veins and loss

of perfusate from the active circulation. The attractiveness of this view resides in the fact that it could account for the drop in cardiac output, particularly during the late phase of shock on the basis of a progressive sequestration of blood in capacitance vessels and extravasation of fluid from capillaries.

The purpose of the present study was to evaluate the possible participation of these mechanisms in experimental septic shock.

METHODS

A total of 51 forelimb experiments was carried out on adult mongrel dogs, anesthetized with sodium pentobarbital, 30 mg/Kg body weight. The study employed six experimental designs as follows: The first series was comprised of four types of studies in which limb segmental resistance responses were correlated with alterations in weight and experiments carried out on innervated or denervated limbs using either endotoxin or live E. coli organisms; a second series explored the possible effects of distending pressure and flow on segmental resistance changes in shock; and a final group of studies was performed on skinned forelimb preparations in which muscle responses were contrasted to the prior experiments with skin intact. E. coli endotoxin (Difco, Detroit) was used at a LD_{100} (3 mg/Kg). Other animals received an LD_{100} ($3\text{-}6 \times 10^9$ organisms/Kg) of live E. coli organisms from the enteropathogenic Dunwald strain typed as 0125:B15, Canioni. Organisms were prepared as described in earlier report (8). Endotoxin or live organisms in saline concentrations of 1 mg/ml and 10^9 organisms/ml, respectively, were injected over a two-minute period into the femoral veins of dogs perfusing their own surgically prepared innervated or denervated forelimbs.

Twenty percent of the animals died within four hours, prior to termination of the experiments, which were designed to continue for five hours.

The limb to be perfused was surgically removed above the elbow by use of double ligatures and cautery so that minimal bleeding occurred. In forelimbs perfused at natural blood flow, the brachial artery intact, all visible nerves were left intact in 15 experiments and were sectioned in 18 studies. Nerves were maintained viable by application of silicone and warmth, and were tested for appropriate vascular responses at termination of experiment. Prior to perfusion, animals were heparinized, 3 mg/kg, and vessels were cannulated. Small artery and small vein pressures were obtained in the paw of the isolated limb by placement of catheters (outside diameter, 0.8 mm) as previsusly described (4, 7), and limbs were placed in a metal support and continuously weighed on a strain gauge weighing device (4). The zero pressure reference catherer tip was positioned at the midpoint of the limb, which was supported in a horizontal position.

Forelimb brachial and cephalic orifice veins were separately cannulated with short large bore polyethylene catheters and drained into a small plastic cylinder immersed in a constant temperature water bath. Large vein orifice pressures were matched and maintained at atmospheric pressure. Flows from both veins were measured with a calibrated cylinder over a timed interval which was varied according to flow rate. Venous blood was continually returned to the femoral vein of the support dog by means of an adjustable pump so that inflow to the limb always equalled return from the organ to the animal. Experiments were begun after an initial equilibration period of approximately one hour and terminated after five hours, or death.

Forelimb vascular resistances were calculated by division into anatomical segments as follows: (a) Large artery resistance (resistance between

the brachial artery and small metacarpal artery); (b) Small vessel resistance (resistance between the small artery and small metacarpal vein); (c) Venous resistance (resistance between small vein and severed brachial and cephalic drainage veins). Resistances were expressed as mm Hg/cc/min and were calculated as follows: Total resistance (R_T) = large artery pressure (orifice brachial artery pressure) divided by limb blood flow; large artery resistance (R_A) = large artery pressure minus small artery pressure divided by limb flow; small vessel resistance (R_{SV}) = small artery pressure minus small vein pressure divided by flow; and venous resistance (R_V) = small vein pressure divided by flow.

During the course of the experiments, it was observed that limb blood flows declined to exceedingly low values at natural flow perfusion (brachial artery intact) in shock. It was therefore decided to investigate the possibility that segmental resistances might have been altered by both passive and active factors. A separate series of nine forelimb studies was therefor carried out identical to the prior group of 33 experiments, except that arterial inflow was produced alternately by a pump at regulation flows, and natural flow dependent on pressure developed by the heart. In this latter group, following onset of shock, flows were natural except at specified intervals when flow was returned to control (pre-shock) values by switching to the pump perfusion system.

Nine additional experiments were completed in the skinned innervated forelimb in order to evaluate the participation of muscle alone in limb weight changes and alterations in total forelimb muscle resistance. Skin was carefully reflected away from muscle and removed, and a tight wire ligature was placed around the wrist. These experiments were particularly

designed to determine if muscle pooling, i.e., accumulation of perfusate intra- and/or extra-vascularly, could account for the development of irreversible systemic hypotension in experimental septic shock.

RESULTS

Figure 1 presents mean pressure results from a total of thirty-three canine forelimb experiments in which limbs were perfused at natural flow from animals injected with lethal doses of live E. coli organisms or endotoxin. Orifice brachial artery pressure, which was essentially equal to mean aortic pressure, initially averaged between 128-133 mm Hg and fell in a similar fashion in all experiments. The average maximum fall to between 55 and 72 mm Hg occurred between one and two hours after injection, followed by a partial recovery not exceeding 100 mm Hg. There was no significant difference in the blood pressure responses of each of the four types of experiments.

Segmental resistance changes. Mean resistance changes have been calculated in three vascular segments, and results are presented in figures 2-4. Large artery resistances, including the vascular segment from orifice brachial artery to small artery in the paw, show similar responses in all forelimbs, innervated or denervated, injected with either live organisms or endotoxin. Early sustained increases in large artery resistance were regularly observed in all experiments within thirty minutes after injection. Although pre-shock resistance values were similar, ranges of responses in the four types of experiments during shock were large. All resistances increased significantly above the controls ($p \leq 0.05$) beyond the third hour to termination of the experiments.

Figure 3 presents small vessel resistance values in the four types of experiments. Small vessel resistances, including the anatomical region from small artery to small vein in the paw, increased markedly on the average, although individual variations were great. Most points on the graph represent changes notably above the pre-shock values ($p \leq 0.05$ third through fifth hours) except the innervated experiments with endotoxin, in which there was such a wide variation of response that significance could not be achieved. In this group, however, four out of the five studies consistently showed values above control throughout the five hour period. Resistances of all four groups were significantly elevated above control values during the first hour after injection ($p \leq 0.05$).

Figure 4 illustrates the finding that venous segment resistance rises markedly above control after injections of live organisms in both innervated and denervated limbs ($p \leq 0.05$) in all observed periods during the shock state. Resistances were also significantly elevated in the endotoxin injected denervated limbs ($p \leq 0.05$). Because of wide variations in response, resistances were insignificantly altered ($p > 0.05$) in innervated organs administered endotoxin. However, in this last series, all individual limb preparations exhibited sustained rises in venous resistance.

Comparison of changes in limb weight and vascular resistance ratios.

The next aim of this study was to determine if there was a way to account for the observed changes in forelimb weight on the basis of alterations in the ratio between pre- and post-capillary vascular resistances. Figure 5 demonstrates the observed finding that all limb preparations progressively decreased in weight during the shock period. Since an increase

in the fraction precapillary/postcapillary resistance might conceivably account for the shrinkage of weight, this relationship was explored in two ways: Figures 6 and 7 show that there are decreases in the ratios of resistance R_{SV}/R_V and $R_A + R_{SV}/R_V$ from one hour to termination of experiments after precipitation of shock. Venous resistance rose so markedly on the average, that ratios were only increased during the initial shock period (< one hour). Since these findings appeared contrary to those expected on the basis of theoretical considerations (2, 10, 13), it was thought that a different pattern might be seen if only those animals dying during the observation period were examined. Table I is presented to show the relationship between limb weight changes and ratios of resistances in forelimbs in animals dying in shock between 2 and 5 hours after injection. Results clearly show that limb weight consistently falls in the presence of a decrease in the ratios of resistance R_{SV}/R_V and $R_A + R_{SV}/R_V$.

An alternative explanation for these unexpected results was then explored and Figure 8 and Table II perform important roles in explaining the observations: Blood flows and pressures in both large and small arteries fell to extremely low values after both live E. coli organism and endotoxin injections, opening the possibility that capillary pressure at natural flow perfusion is markedly lower than control (pre-shock) values even in the face of intense venous constriction.

An evaluation of passive and active components of resistance.

A surprising finding in the present study was the markedly elevated large vessel resistance in the forelimb. Since distending pressures and flows were greatly reduced following induction of shock, it was thought

that a passive diminution of vessel bore diameter might directly bring about a a rise of vascular resistance. A separate series of experiments was therefore designed to evaluate this possibility, and findings are shown in Figure 9. Calculated segmental resistances were higher on the average at natural flow perfusion, as indicated by the solid lines on the figure which represents mean values for nine experiments. These experiments, in which limb blood flow fell markedly, show that when flow is returned to the pre-shock values (dashed lines), resistances are lower in each limb resistance segment. Individual spread of values prevented statistical significance ($0.10 > p > 0.05$) when means were compared at each time interval for the portion of the figure depicting large artery and small vessel resistances. Resistances however consistently fell in all individual experiments when flow was restored to control pre-shock values. Differences in venous resistance were significant ($p = 0.05$) at the 1, 2, and 4 hour periods.

Weight and resistance changes in forelimb muscle preparation.

Since the possibility existed that opposite weight changes were occurring in skin (a loss) and muscle (a gain) after live E. coli organism or endotoxin injections, a separate series of experiments was designed to evaluate the possible role of muscle pooling in shock.

The average results from nine dog-perfused skinned forelimb experiments are shown in Figure 10. Results show that the muscle preparation exhibits average weight and total resistance changes in the shocked state similar to the non-skinned preparations.

DISCUSSION

A major problem in endotoxin shock is the question of the possible role of generalized peripheral pooling of blood in the development of the

irreversible state. An attractive hypothesis would be that, just as the hepatosplanchnic region serves as a site of pooling in the early phase of shock (5, 11, 12, 14), a steady loss of blood or ultrafiltrate into other tissues such as skin and muscle, would explain the later detrimental hemodynamic defect (2, 13). In support of this possibility are earlier reports revealing a decrease in venous return and pooling in eviscerated dogs receiving endotoxin (3); a gain in limb weight in constant flow perfusion studies (4); and a thesis offered by others (2, 13), suggesting a major role of capacitance vessels in trapping blood and transudation of fluid into muscle tissue leading to the precipitation of irreversible shock after hemorrhage. The possibility of such a mechanism operating in shock is worthy of serious consideration since it was calculated (13) that a 70 kg man in hemorrhagic shock could lose 600 ml/hr from the circulating blood volume by filtration into his muscle mass.

The current study was designed to measure limb weight changes and to observe alterations in limb segmental resistances in the dog to ascertain if systemic hypotension in experimental septic shock could be accounted for by alterations in the resistance ratios between the pre- and post-capillary segments (13). It was considered important to evaluate the relative role of neurocefferent stimuli and circulating humoral substances in the forelimb response. Two types of experimental lethal septic shock were studied: One was elicited by intravenous injections of live E. coli organisms and the second was precipitated by the administration of E. coli endotoxin.

Results from the present study offer no evidence that loss of circulating blood or its constituents into skin or muscle could explain the development of sustained systemic hypotension on the basis of a progressively

decreased venous return. On the contrary, absence of pooling in the forelimb was consistently observed in the experimental models employed in the present study, and perfusate was continuously yielded from the limb into the venous effluent to be mobilized into the actively circulating blood volume. Results from the present study, therefore, provide no evidence for the participation of skin and muscle pooling of blood or accumulation of tissue fluid in the development of irreversible septic shock.

It is clear from these findings that the canine species may die in septic shock with shrunken limb volumes, and therefore other as yet unknown mechanisms must be identified in order to explain the development of irreversibility. It is of interest that limbs responded in a qualitatively similar fashion whether shock was elicited by live organisms or endotoxin. This observation gives support to the assumption that endotoxin may be the active component following injection of live E. coli organisms. Endotoxin injected intra-arterially in a pump-lung blood perfused foreleg (minus the remainder of the animal) elicits only negligible vascular responses (4). Neurohumoral factors appear to compose the primary potent stimuli in the elicitation of limb vascular responses. The present study appears to provide support for the view that circulating vasoconstrictor agents are performing a more prominent role than peripheral nerve stimuli in this form of shock (4,6). Although catecholamine-like in action, their exact identity is unknown (6). It should be noted, however, that although the degree of vasoconstriction observed in the present study was similar in both innervated and denervated limbs, the latter were in a relatively more dilated state prior to injection of E. coli organisms or endotoxin as revealed by higher initial flow rates (Table II). The presence of a pre-existing state of dilatation in the

denervated limbs may therefore have permitted a more ready expression of vasoconstriction in response to circulating vasoactive agents. Additionally, it has been shown by others that changes in segmented vascular resistances in the dog paw differ following nerve stimulation as opposed to catecholamine administration (1). It was found that while norepinephrine caused marked constriction of small vessels in the paw, nerve stimulation elicited a lesser degree of constriction (1).

The markedly depressed blood flow in all forelimbs in both skin and muscle regions, as noted in the present experiments, is explained on the basis of greatly lowered arterial perfusion resulting from systemic hypotension and rapidly developing pre-capillary vasoconstriction. Two possibilities appear to emerge from this action: First, greatly lowered flows may result in a failure to provide normal metabolic requirements of limb tissue, thus bringing about the release of various biochemical products of metabolism into the limb venous effluent. These substances may be detrimental to other organs in the animal and may presumably contribute to the development of acidosis commonly observed (6,11,13). Secondly, the greatly lowered blood flow in the presence of sustained pre-capillary vasoconstriction most probably results in a very low capillary pressure in the forelimb, even in the presence of prominently sustained venoconstriction. Thus, even though the percentage rate of increase of the venous segment resistance exceeds those of all other limb vascular segments, limb weight persistently remains below that of the control, pre-shock preparation. Findings also indicate that the increases in small vessel and venous segment resistances are due to both active and passive vasoconstriction, the latter resulting from passively diminished vessel diameters because of decreased distending

pressure and flow. The mechanism postualted by others (2, 13) accounting for limb pooling in hemorrhagic shock because of a decreased pre- to post-capillary resistance ratio, cannot be employed to explain the results of the present study.

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Table I

Relationship of limb weight changes and ratios of resistance in animals dying in E. coli organism* or endotoxin** shock

	Expt. #	0	0.5	1	2	3	4
Large Artery Pressure (mm Hg)	1*	120	77	45	60	76	85
	2*	133	62	57	87	-	-
	3*	135	91	43	55	63	60
	4*	127	50	35	35	-	-
	5*	126	89	80	46	65	70
	6*	128	60	49	33	38	-
	7**	150	97	46	-	-	-
	8**	132	58	36	34	25	-
	9**	102	68	42	46	25	-
Mean		128	72	48	50	49	72
Δ Limb Weight (gms)	1	-	-2.5	-3.5	-	+7.5	+10.0
	2	-	-12.5	-16.3	-17.5	-	-
	3	-	-6.5	-12.0	-14.0	-13.0	-11.0
	4	-	-12.5	-19.0	-26.0	-	-
	5	-	-4.6	-5.3	-10.5	-11.5	-11.0
	6	-	-6.5	-9.0	-13.0	-17.0	-
	7	-	-4.5	-9.0	-11.0	-	-
	8	-	-15.0	-17.0	-17.5	-22.0	-
	9	-	-7.0	-10.0	-12.0	-13.0	-
Mean			-7.9	-11.2	-13.5	-11.5	-4.0
R_{SV}/R_V	1	10.81	9.54	3.43	1.79	2.36	1.08
	2	11.56	6.51	6.38	3.24	-	-
	3	7.63	7.08	1.86	3.78	4.38	2.76
	4	10.83	8.50	5.75	6.05	-	-
	5	2.00	2.37	1.64	.58	2.22	1.61
	6	7.50	3.11	2.11	2.28	2.11	-
	7	12.58	9.56	7.63	-	-	-
	8	3.16	3.85	1.97	1.74	.22	-
	9	4.56	11.00	6.43	3.00	2.77	-
Mean		7.85	6.84	4.13	2.81	2.34	1.82
$R_A + R_{SV}/R_V$	1	13.19	11.50	5.43	7.40	9.26	6.06
	2	13.75	7.78	8.57	4.51	-	-
	3	9.51	10.67	5.41	7.21	7.08	6.52
	4	12.92	11.50	7.75	7.83	-	-
	5	5.65	5.83	5.03	2.83	3.65	3.26
	6	13.50	5.67	4.44	3.70	3.22	-
	7	16.25	17.30	14.38	-	-	-
	8	6.21	6.81	4.62	4.48	2.05	-
	9	7.48	12.60	7.43	3.60	3.72	-
Mean		10.93	9.96	7.01	5.20	4.83	5.28

Table II

Percent Change in Brachial and Cephalic Vein Blood Flows in Innervated and Denervated Canine Forelimbs after live *E. coli* or Endotoxin Injections

Experiment	Mean Initial Values ± SE (cc/min)	Mean percent change in flows: Hours Post-injection					
		+0.5	1	2	3	4	5
E. coli Organisms							
Innervated limbs							
Brachial	35 ± 4	-60	-70	-56	-57	-51	-48
Cephalic	25 ± 4	-45	-70	-73	-73	-86	-69
Denervated limbs							
Brachial	58 ± 8	-58	-80	-82	-81	-75	-82
Cephalic	32 ± 8	-60	-70	-69	-76	-77	-84
Endotoxin							
Innervated limbs							
Brachial	27 ± 10	-61	-62	-60	-38	-22	-30
Cephalic	28 ± 8	-80	-77	-72	-65	-70	-73
Denervated limbs							
Brachial	50 ± 9	-85	-86	-77	-69	-65	-67
Cephalic	40 ± 6	-82	-83	-84	-86	-92	-89

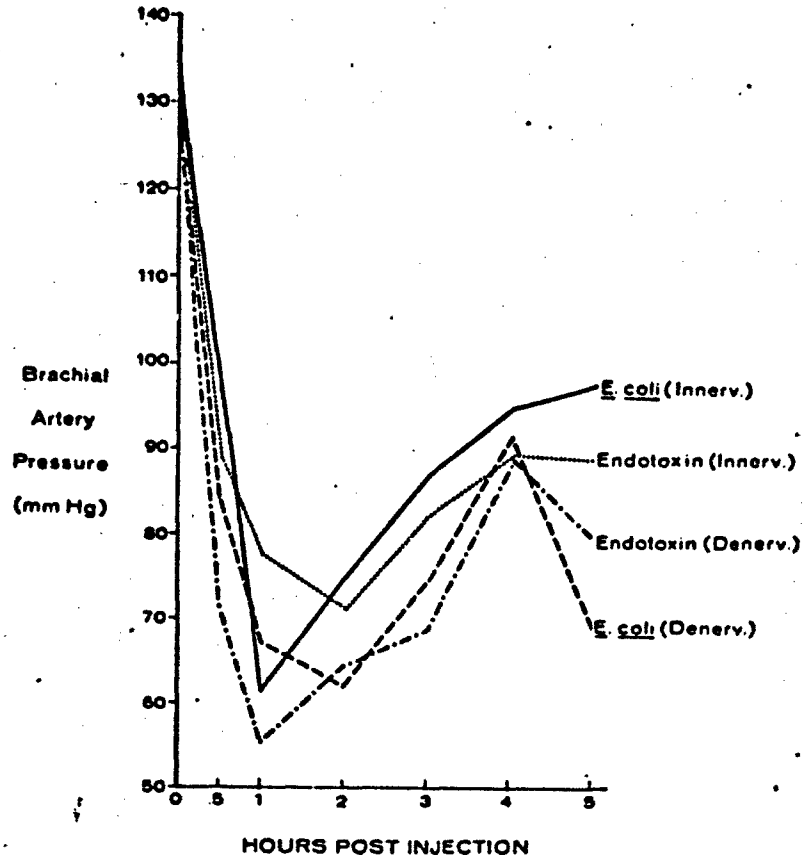

Figure 1. Changes in brachial arterial perfusion pressure following injection of E. coli organisms or endotoxin in innervated and denervated canine forelimb. Mean values: Endotoxin, innervated (N = 5); endotoxin, denervated (N = 9); E. coli live organisms, innervated (N = 10); E. coli organisms, denervated (N = 9).

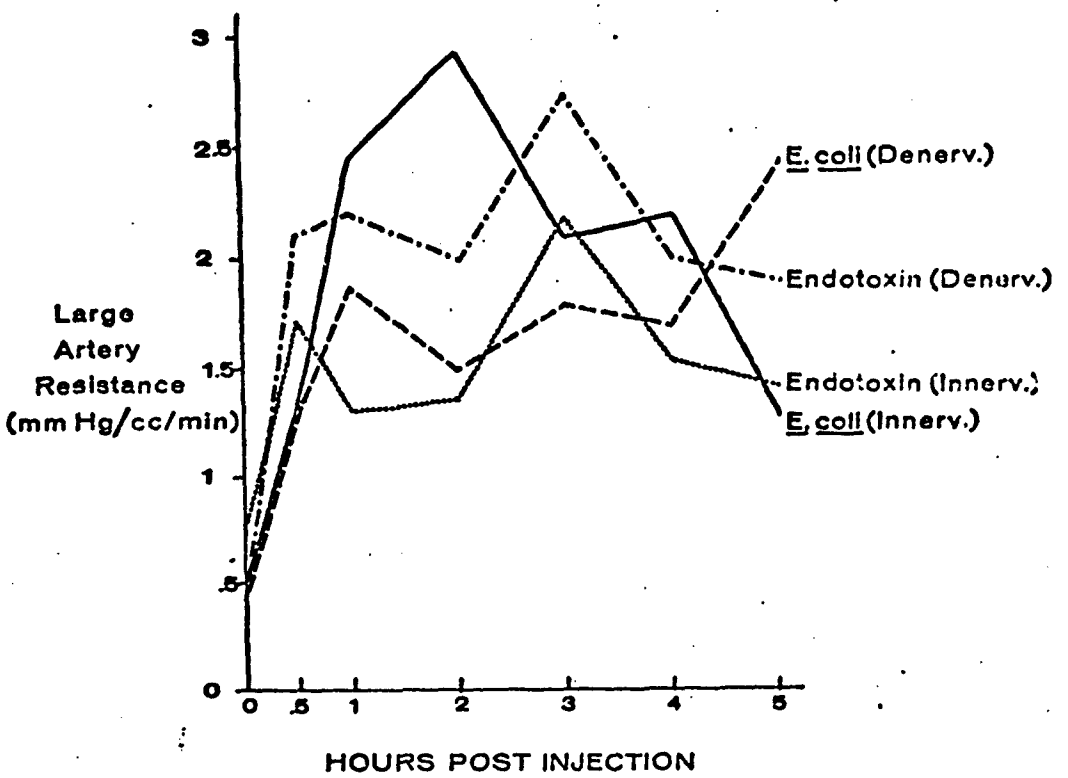

Figure 2. Alterations in large vessel resistance in the forelimb after E. coli organisms or endotoxin. Mean values; Endotoxin, innervated (N = 5); endotoxin, denervated (N = 9); E. coli live organisms, innervated (N = 10); E. coli organisms, denervated (N = 9).

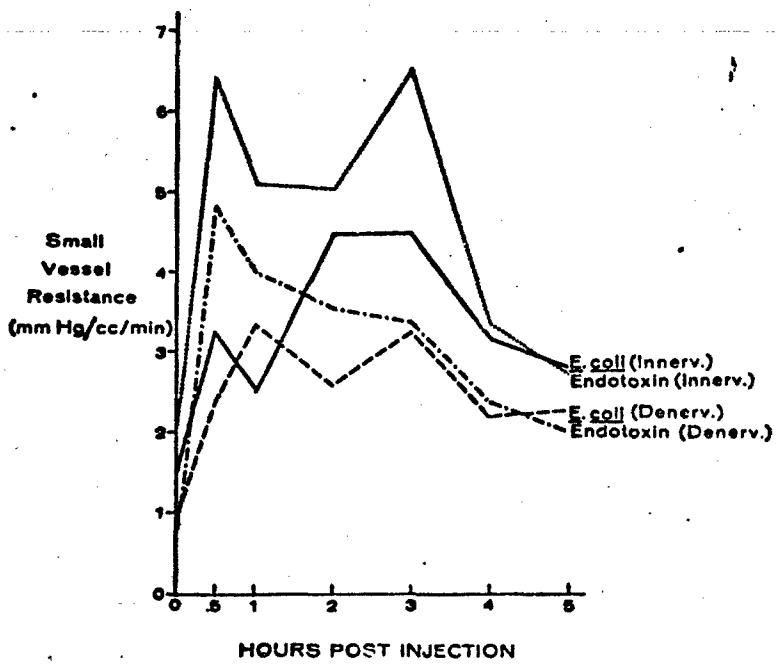

Figure 3. Alterations in small vessel resistance in the forelimb after E. coli organisms or endotoxin. Mean values; Endotoxin, innervated (N = 5); endotoxin, denervated (N = 9); E. coli live organisms, innervated (N = 10); E. coli organisms, denervated (N = 9).

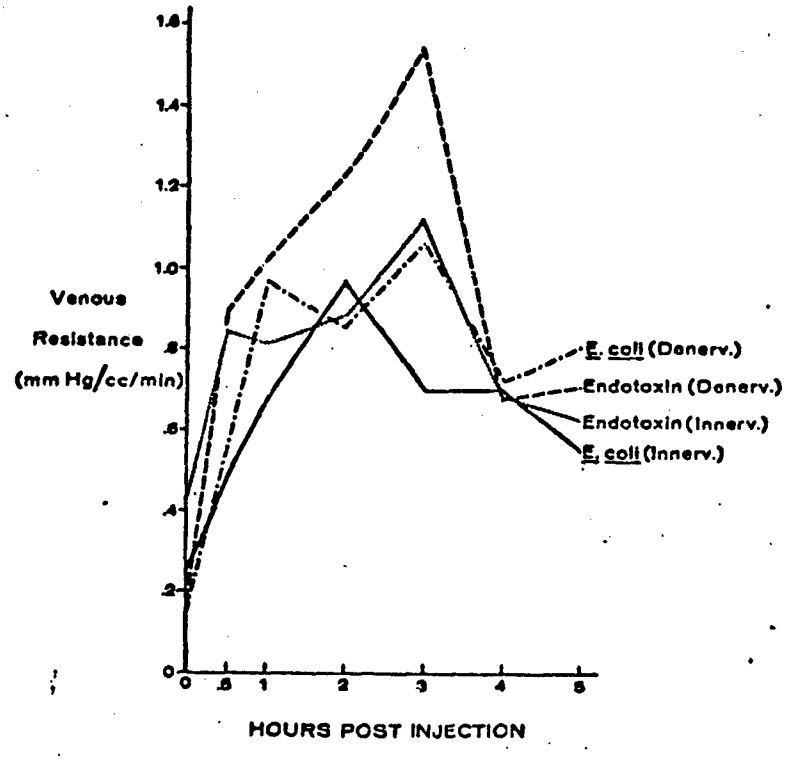

Figure 4. Alterations in venous resistance in the forelimb following administration of live organisms or endotoxin. Mean values; Endotoxin, innervated (N = 5); endotoxin, denervated (N = 9); E. coli live organisms, innervated (N = 10); E. coli organisms, denervated (N = 9).

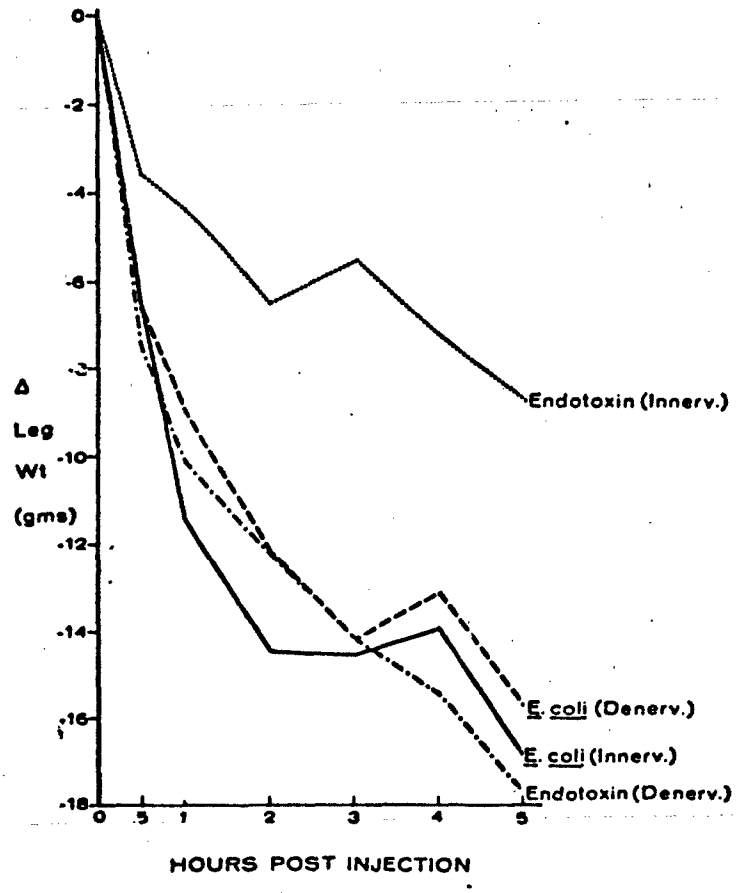

Figure 5. Changes in limb weight after administration of live organisms, or endotoxin, in innervated and denervated preparations. Mean values.

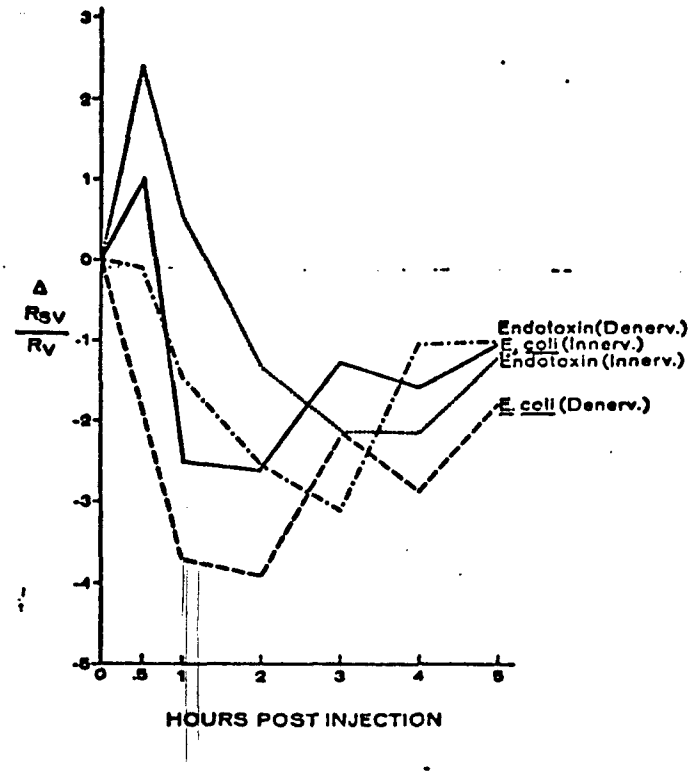

Figure 6. Changes in small vessel to venous resistance ratios after endotoxin or live organisms. Mean values.

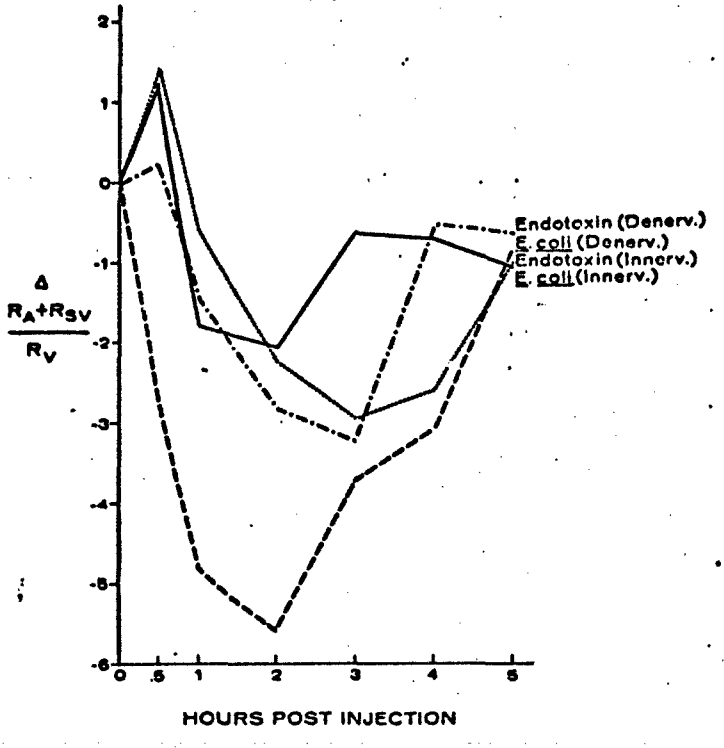

Figure 7. Changes in pre-capillary to venous resistance ratios after live E. coli organisms or endotoxin. Mean Values.

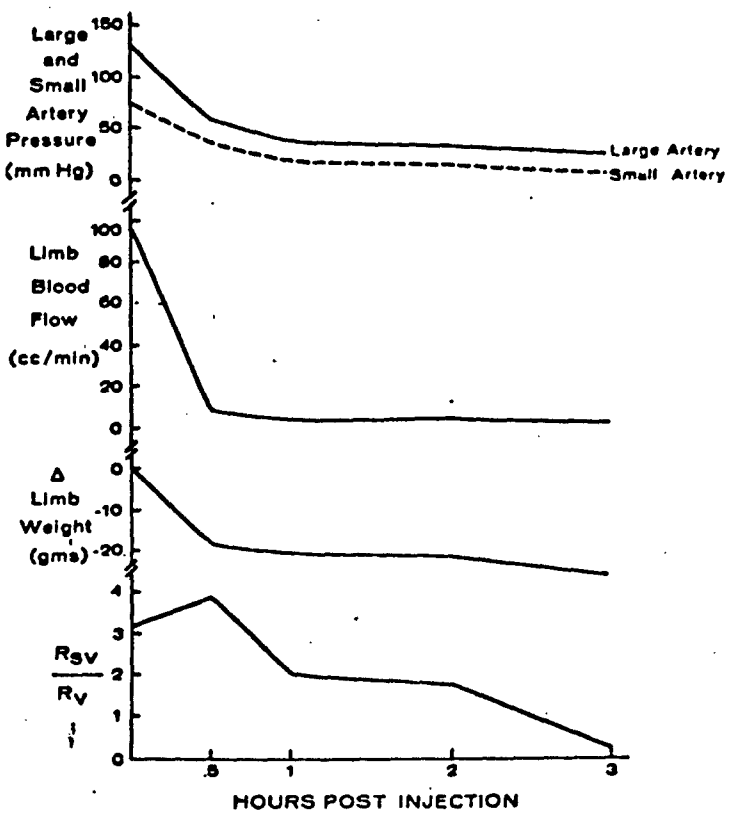

Figure 8. Vascular and limb weight responses of animal dying in endotoxin shock.

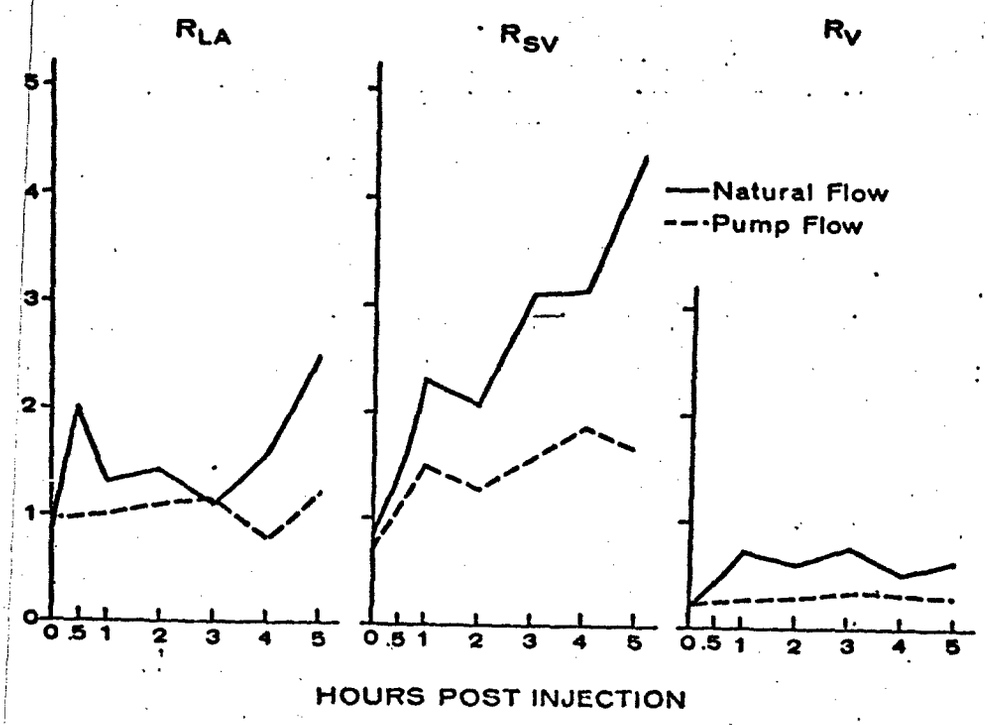

Figure 9. A comparison of passive and active components of resistance in various forelimb segments after injection of live *E. coli* organisms or endotoxin. Mean values (N = 9).

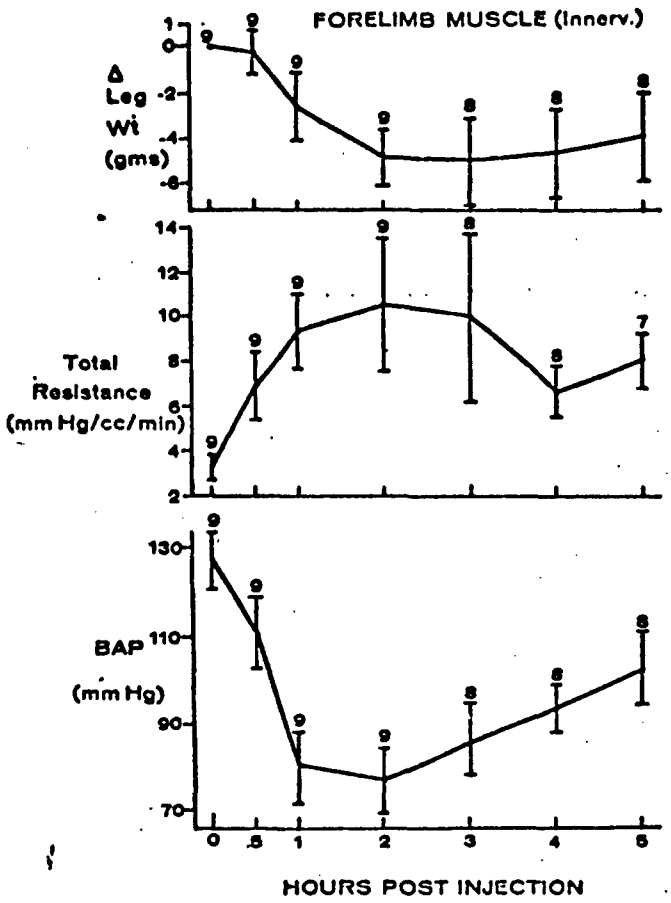

Figure 10. Changes in forelimb muscle weight and resistance after injection of live E. coli organisms or endotoxin. Mean values (N = 9).

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(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author) MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.	2a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED 2b. GROUP UNCLASSIFIED

3. REPORT TITLE

CORRELATION OF POOLING AND RESISTANCE CHANGES IN THE CANINE FORELIMB IN SEPTIC SHOCK

4. DESCRIPTIVE NOTES (Type of report and, inclusive dates)

Technical Report

5. AUTHOR(S) (First name, middle initial, last name)

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6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
December 21, 1970	30	13

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
N00014-68-A-0496 b. PROJECT NO. NR 105-516 c. d.	34 9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)

10. DISTRIBUTION STATEMENT

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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Office of Naval Research

13. ABSTRACT

A major problem in endotoxin shock is the role of peripheral pooling of blood in the development of the irreversible state. The present study was designed to determine if there was a causal relationship between pre- and post-capillary resistance changes in the canine forelimb and later peripheral pooling. Experiments were carried out on innervated and denervated forelimbs perfused by anesthetized animals administered lethal injections of live E. coli organisms or endotoxin. Absence of pooling in the forelimb was consistently noted and perfusate was continuously yielded from the limb into the venous effluent, even in the presence of a decreased pre- to post-capillary resistance ratio. Animals were observed to die with shrunken limb volumes presumably resulting from decreased perfusion pressure and active pre-capillary constriction. Severely depressed flow rates and distending pressures produced increases in small vessel and venous segment resistances on a passive basis. Results offer no evidence that loss of circulating blood into skin and muscle may account for the development of systemic hypotension in experimental septic shock.